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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/698,354	10/30/2003	David James Rawson	PC25373A	1622

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Warner-Lambert Company LLC
2800 Plymouth Road
Ann Arbor, MI 48105

EXAMINER

ROYDS, LESLIE A

ART UNIT	PAPER NUMBER
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1614

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/698,354	RAWSON, DAVID JAMES	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 August 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 11-26 is/are pending in the application.
- 4a) Of the above claim(s) 15-26 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 11-14 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date: _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date: _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Claims 11-26 are presented for examination.

Applicant's Amendment filed August 16, 2006 has been received and entered into the present application.

Claims 11-26 are pending. Claims 1-10 are cancelled, claims 11-12 are amended and claims 14-26 are newly added.

Applicant's election with traverse of the Invention of Group II (original claims 9-13), directed to compounds and pharmaceutical compositions or combinations thereof, and the election of the species of (2S, 4S)-4-(3-fluorobenzyl)-pyrrolidine-2-carboxylic acid as the compound to be examined (which correlates to generic formula (Ib), in the papers submitted February 24, 2006, is acknowledged.

Examination of the elected species of compound has determined that the prior art was such at the time of the invention that it did not teach or suggest such a compound. However, search and examination of the present claims has been expanded to now read upon compounds corresponding to generic formula (Ia). Claims 11-14 are readable on such compounds and are herein under examination. Claims 15-26 remain withdrawn from consideration pursuant to 37 C.F.R. 1.142(b).

Applicant's arguments, filed August 16, 2006, have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Claim Rejections - 35 USC § 112, First Paragraph, Written Description Requirement

(New Grounds of Rejection)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode

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contemplated by the inventor of carrying out his invention.

Claim 13 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Present claim 13 is directed to a combination comprising a compound of formula (Ia) according to claim 14, or a pharmaceutically acceptable salt thereof, and at least one other therapeutically active agent, which is a PDEV inhibitor.

In particular, the specification as originally filed fails to provide adequate written description for the genus of PDEV inhibitors (claim 13).

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to the MPEP §2163. In particular, *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plain for obtaining the claimed chemical invention." *Eli Lilly*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for *Examination of Patent Applications* under the 35 U.S.C. 112.1 "Written Description" Requirement ("*Guidelines*"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter alia*, "functional characteristics when coupled with a known or disclosed correlation between function and structure..." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting *Guidelines*, 66 Fed. Reg. at 1106 (emphasis added)). Moreover, although *Eli Lilly* and *Enzo* were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co.*, 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

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Applicant discloses at the paragraph bridging pages 28-29 of the instant specification, “xx) PDEV inhibitors, e.g. sildenafil, vardenafil (Bayer), tadalafil (Icos Lilly), 1-{6-ethoxy-5-[3-ethyl-6,7-dihydro-2-(2-methoxyethyl)-7-oxo-2H-pyrazolo[4,3-d]-pyrimidin-5-yl]-3-pyridylsulfonyl}-4-ethylpiperazine, 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidiny)-2,6-dihydro-7H-pyrazolo-[4,3-d]-pyrimidin-7-one and 5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulfonyl)pyridine-3-yl]-3-ethyl-2-[2-methoxyethyl-2,6-dihydro-7H-pyrazolo-[4,3-d]-pyrimidin-7-one.”

While such disclosure has been acknowledged, it is noted that the disclosed PDEV inhibitors are merely exemplary and non-limiting. Applicant has failed to provided a limiting definition via the disclosure of relevant structural characteristics or physical properties, aside from the generic function of being a PDEV inhibitor, that would provide adequate written description of the genus of compounds capable of performing such a function that Applicant was actually in possession of, and intended to be used within the context of the present invention, at the time of the invention.

MPEP §2163 recites, “The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the Applicant was in possession of the claimed genus.” Please reference *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Though it is noted that the instant specification provides exemplification of those compounds that inhibit PDEV, it remains that Applicant has failed to define any structural component, such as a common core structural element, as being responsible for the function of the compound in inhibiting PDEV and, thus, has failed to define the metes and bounds of the genus. While it is duly noted that the genus of compounds that inhibit PDEV is clearly limited to those capable of functioning in this manner, it remains

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that Applicant has not appropriately defined the metes and bounds of the genus, even when limited by function (step-plus-function form). MPEP §2163 teaches that step-plus-function claims are adequately described if “the written description *adequately links or associates adequately described particular structure, material, or acts to the function recited in a step-plus-function claim limitation,*” or if “it is clear based on the facts of the application that one skilled in the art would have known what structure, material, or acts perform the function recited in a step-plus-function limitation.” The instant application does not meet either of these criteria. The present specification provides no disclosure beyond the generic disclosure of the required function and certain exemplary compounds that would provide a means for identifying the compounds that would have been amenable for use in the present invention, nor does it specifically teach a common structural element that performs the function recited in the claim and would be readily identifiable to one of skill in the art. Furthermore, it has been held that a wish or plan for obtaining the chemical invention as claimed does not provide adequate written description of a chemical invention. Rather, a precise definition, such as by structure, formula, chemical name or physical properties or a combination thereof, is required. Please reference, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004).

While it is recognized that adequate written description of a limitation is not required to be stated *in haec verba* in the specification or claims as originally filed, adequate written support for claim limitations must arise from either an explicit or implicit suggestion by the disclosure to show that such a concept as claimed was actually in possession of Applicant at the time of the invention. For the reasons provided *supra*, Applicant has failed to provide the necessary teachings, by describing the claimed invention with all of its limitations using such descriptive means that fully set forth the claimed invention, in such a way as to reasonably convey to one skilled in the relevant art that Applicant had possession of the entire genus of compounds capable of inhibiting PDEV.

Accordingly, the claims are considered to lack sufficient written description and are properly

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rejected under 35 U.S.C. 112, first paragraph.

Claim Rejections - 35 USC § 102 (New Grounds of Rejection)

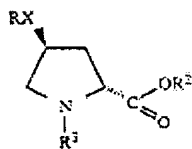
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 14 is rejected under 35 U.S.C. 102(b) as being anticipated by Kyle et al. (U.S. Patent No. 5,385,889; 1995).

Kyle et al. discloses the preparation of an intermediate chemical entity and its use to prepare a bradykinin antagonist peptide, which has the following chemical formula (col.6, l.34-44 and col.20, l.35-61):



, wherein R is an aryl group, a substituted aryl group or an arylalkyl group, X is oxygen (col.20, l.49-52) and R₂ and R₃ are each hydrogen (col.20, l.56-59). Kyle et al. defines “aryl” groups as benzene, phenyl or naphthyl and “substituted aryl” groups as a substituted aromatic ring with nitro substitution or halogen substitution (col.20, l.66-col.21, l.2).

Claim Rejections - 35 USC § 103 (New Grounds of Rejection)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

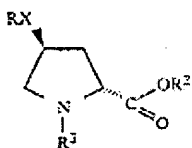
(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

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having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 11-12 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kyle et al. (U.S. Patent No. 5,385,889; 1995).

Kyle et al. discloses the preparation of an intermediate chemical entity and its use to prepare a bradykinin antagonist peptide, which has the following chemical formula (col.6, l.34-44 and col.20, l.35-61):



, wherein R is an aryl group, a substituted aryl group or an arylalkyl group, X is oxygen (col.20, l.49-52) and R² and R³ are each hydrogen (col.20, l.56-59). Kyle et al. defines “aryl” groups as benzene, phenyl or naphthyl and “substituted aryl” groups as a substituted aromatic ring with nitro substitution or halogen substitution (col.20, l.66-col.21, l.2).

The differences between the subject matter sought to be patented and the prior art of Kyle et al. are that the reference does not *expressly* teach the combination of the disclosed intermediates with one or more pharmaceutically acceptable excipients, diluents or carriers (claim 11) or the combination of the disclosed compounds with at least one other therapeutically active agent (claim 12).

However, these differences are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains because Kyle et al. expressly discloses the above compounds as isolated intermediate compounds for use in the preparation of the final bradykinin antagonist peptide product (col.20, l. 35-61) and further discloses exemplary synthetic schema for producing the proline substituent at position-7 of the disclosed bradykinin peptide, using reactants such as sodium hydroxide, etc. (col.22, l. 37-col.23, l.10). It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention that the use of such an isolated intermediate chemical entity for use in the preparation of a peptide product would require

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the reaction of such an intermediate chemical product with, for example, an alkali or alkaline earth metal hydroxide as exemplified in Kyle et al., or another excipient, diluent or carrier, in order to form the final hydroxyproline substituent for position-7 of the bradykinin peptide. Kyle et al. further supports this conclusion by explicitly stating that the disclosed intermediate compounds are used in the preparation of the bradykinin antagonist peptides (col.20, lines 35-61), which implicitly suggests the combination of the intermediate with another active compound to produce the final product.

Furthermore, it would also have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention that execution of conventional methods of peptide synthesis would have necessarily included the step of reacting the bradykinin peptide *per se* (i.e., a therapeutically active agent) with the disclosed intermediates for producing the disclosed modified bradykinin antagonist peptide with the hydroxyproline substituent at position-7.

Response to Applicant's Arguments

Applicant traverses the application of Kyle et al. as prior art against the claims, stating that Kyle et al. teaches the cited compounds as process intermediates and are not described as bradykinin antagonists. Applicant further argues that Kyle et al. cannot be relied upon to teach or suggest making the compounds claimed in the present application, which are alpha-2-delta ligands. Applicant relies upon *In re Jean Pierre Lahu and Louis Foulletier*, 747 F.2d 703, 707 (Fed. Cir. 1984), and states that nothing in Kyle et al. indicates the proline intermediates are themselves bradykinin antagonists.

Applicant's traversal has been fully and carefully considered in its entirety, but fails to be persuasive.

First, it is noted that, regardless of the fact that Kyle et al. may disclose the compounds of the formula identified *supra* as intermediate products, it remains the such compounds are *structurally identical* to those that Applicant has presently claimed within generic formula (Ia). Accordingly, the fact

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that Kyle et al. does not disclose them as antagonists of bradykinin or as having the alpha-2-delta ligand activity as Applicant has discovered is immaterial to the fact that Kyle et al. has expressly isolated and identified compounds of the identical chemical structure as those presently claimed (see, e.g., present claim 14). Products of identical composition cannot have mutually exclusive properties, so whatever alpha-2-delta ligand activity that Applicant has presently attributed to the claimed compounds is necessarily present in the compounds expressly isolated and disclosed by Kyle et al., whether recognized by the patentee or not. Please reference MPEP §2112. In addition, the fact that Applicant's utility may differ from the utility disclosed in Kyle et al. is immaterial to the fact that the reference discloses (1) compounds of the exact and identical chemical structure to those presently claimed and (2) a specific and substantial utility for such compounds. In view of such disclosure, Kyle et al. properly anticipates the presently claimed invention, absent factual evidence to the contrary.

Further, Applicant is reminded that, at the very least, present claim 14 is directed solely to a "compound" and does not require any pharmaceutical acceptability for, for example, direct administration to a host. In view of this, the claim is clearly properly anticipated by the prior art of Kyle et al., who expressly sets forth compound of identical chemical structure to those presently claimed.

Similar rationale applies to present claims 11 and 12, which are, respectively, directed to a "pharmaceutical composition" or a "combination". Regarding present claim 11, the very nature of the fact that the disclosed and isolated intermediates of Kyle et al. are used in a process of forming a bradykinin peptide for pharmaceutical use necessarily meets the requirement of a "pharmaceutical composition", because the combination of the disclosed intermediates with, for example, the disclosed sodium hydroxide reagents, during a pharmaceutical formulation process is clearly a "pharmaceutical composition". Regarding present claim 12, the very nature of reacting the disclosed intermediate compounds with the disclosed bradykinin peptide compounds clearly meets the limitation directed to a "combination" of two agents, absent factual evidence to the contrary.

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Applicant reliance upon *In re Jean Pierre Lalu and Louis Foulletier*, 747 F.2d 703, 707 (Fed. Cir. 1984) has been fully and carefully considered, but is not persuasive. It is noted that each case before the Patent Office is decided on its own merits and in preponderance of the evidence, amendments and arguments presented in each unique case. Decisions made in previous cases before the Office or to the higher courts are not necessarily binding to the course of prosecution. Therefore, Applicant's reliance upon *Lalu* in support of their assertion that the claims are non-obvious over Kyle et al. has been considered, but is not persuasive. This case involved a distinctly different fact pattern from the present case and, therefore, cannot be relied upon to direct the decisions made during prosecution of the present application.

That being said, however, Applicant is reminded that *Lalu* is insufficient to support the allegation that Kyle et al. does not apply as prior art to the claimed compounds because the rejection presented in *Lalu* was based upon structural obviousness, and not structural anticipation. The Examiner in *Lalu* rejected the claims based upon structural obviousness because the prior art of Oesterling taught *homologous* compounds. The Examiner argued that Oesterling disclosed a single method of preparing the disclosed sulfonic acids that required the use of the halide intermediate and further stated that one motivated to prepare the homologous acid would have been similarly motivated to prepare the homologous acid halide.

This is clearly not what is being asserted in the record in the instant case. Kyle et al. anticipates the claimed compounds on the grounds of exact structural identity, not structural homology. In view of the clear, deliberate and unequivocal isolation and identification of the intermediate compounds in Kyle et al., the decision rendered in *Lalu* is not relevant to the present conclusions of anticipation or obviousness because the rejection(s) do not allege the obviousness of a structural modification to the compounds disclosed by the reference to arrive at the compounds presently claimed by Applicant. The compounds of the prior art and those of Applicant are structurally identical and, therefore, Kyle et al. properly

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anticipates and renders obvious Applicant's claimed invention.

For these reasons, and those provided *supra*, rejection of claims 11-12 and 14 is proper and is **maintained**.

Conclusion

Rejection of claims 11-14 is proper.

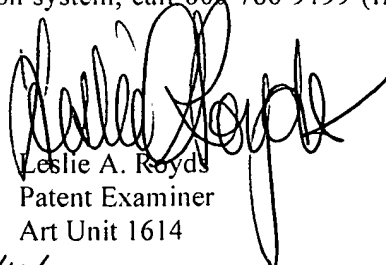
Claims 15-26 are **withdrawn** from consideration pursuant to 37 C.F.R. 1.142(b).

No claims of the present application are allowed.

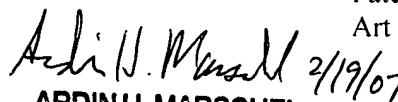
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Leslie A. Royds
Patent Examiner
Art Unit 1614



ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER

February 17, 2007